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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,205	11/14/2006	Nicholas S. Bodor	005612-000024	4092

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EXAMINER	
LAU, JONATHAN S	

ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
03/30/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/551,205	BODOR ET AL.	
	Examiner	Art Unit	
	Jonathan S. Lau	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,8,9,11-14,20,21,23-28,32,33,35,56,57,63,64 and 67-98* is/are pending in the application.

4a) Of the above claim(s) *13,14,20,21,23-28,32,33,35 and 67-81* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 8, 9, 11, 56, 57, 63, 64 and 82-98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1 pg / 16 Dec 2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is responsive to Applicant's Amendment and Remarks, filed 16 Dec 2009.

This application is the national stage entry of PCT/US04/09387, filed 26 Mar 2004; and claims benefit of provisional application 60/458,922, filed 28 Mar 2003; and claims benefit of provisional application 60/484,756, filed 02 July 2003; and claims benefit of provisional application 60/541,247, filed 04 Feb 2004.

The filing date of the instant claims 12, 83, 85 and 89 are deemed to be the filing date of the instant application which is the filing date of PCT/US04/09387, 26 Mar 2004. The filing date of instant claims 1, 2, 8, 9, 11, 56, 57, 63, 64, 82, 84 and 86-98 are deemed to be the filing date of provisional application 60/541,247, filed 04 Feb 2004.

Claims 1, 2, 8, 9, 11-14, 20, 21, 23-28, 32, 33, 35, 56, 57, 63, 64 and 67-98 are pending in the current application. Claims 13, 14, 20, 21, 23-28, 32, 33, 35 and 67-81, drawn to non-elected inventions, are withdrawn. Claims 1, 2, 8, 9, 11, 56, 57, 63, 64 and 82-98 are examined on the merits herein.

Rejections Withdrawn

Applicant's Remarks, filed 16 Dec 2009, with respect to claims 1, 2, 8, 9, 11, 56, 57, 63, 64 and 82-98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schultz et al. (US Patent 6,194,395, published 27 Feb 2001, of record) in view of Wrenn

Jr. (US Patent 6,174,873, issued 16 Jan 2001, cited in PTO-892) and in view of Loftsson et al. (US Patent 6,699,849, filed 16 Feb 1999, cited in PTO-892) has been fully considered and is persuasive, as Applicant is persuasive that one of ordinary skill in the art would not have a reasonable expectation of success in combining the teaching of Wrenn Jr. drawn to a an amorphous formulation using a polymer cross-linked technology with the teaching of Schultz et al. drawn to a solid pharmaceutical oral dosage form of cladribine comprising cladribine and cyclodextrin.

This rejection has been **withdrawn**.

The following are new grounds of rejection not necessitated by Applicant's Amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Amended Claims 1, 2, 8, 9, 11, 56, 57, 63, 64 and 82-98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schultz et al. (US Patent 6,194,395, published 27 Feb 2001, of record) in view of Pitha (US Patent 4,727,064, issued 23 Feb 1988, provided by Applicant in IDS mailed 4 Apr 2008) and in view of Loftsson J Pharm Sci 2002 (Journal of Pharmaceutical Sciences, 2002, 91(11), p2307-2316, cited in PTO-892).

Schultz et al. discloses a solid pharmaceutical oral dosage form of cladribine comprising cladribine and cyclodextrin (column 2, lines 31-39). Schultz et al. teaches β-cyclodextrins are known to possess the ability to form inclusion complexes and to have concomitant solubilizing properties (column 2, lines 10-15). Schultz et al. discloses the use of β-cyclodextrins (column 2, lines 56-58) and derivatives wherein one or more cyclodextrin hydroxy groups are replaced with groups such as hydroxypropyl (column 3, lines 26-27). Schultz et al. discloses the solid oral dosage form in the form of a tablet (column 5, lines 37-38) including the excipients sorbitol and magnesium stearate (column 6, lines 2-7). Schultz et al. discloses an oral dosage form comprising up to 15 mg cladribine and cyclodextrin from 100 to 500 mg, which renders obvious to one of skill in the art the sub-range of a cladribine to cyclodextrin ratio ranging from 15 mg:100 mg to 15mg:500 mg, or 1:6.67 to 1:33.3 by weight (column 6, lines 23-31). Schultz et al. implicitly discloses an oral dosage form comprising up to 15 mg cladribine and cyclodextrin from 100 to 500 mg, or a cladribine to cyclodextrin ratio ranging from 1:6.67 to 1:33.3 by weight (column 6, lines 23-31).

Schultz et al. does not specifically disclose the composition comprising no significant amount of free crystalline cladribine therein (instant claims 1). Schultz et al. does not specifically disclose the composition corresponding to a point located on the curve of a phase solubility diagram for saturated complex cladribine-cyclodextrin complexes, said curve defining complex saturated complexes of cladribine in varying concentrations of the cyclodextrin (instant claim 11). Schultz et al. does not specifically disclose the complex consisting of (a) an amorphous inclusion complex of cladribine

with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex (instant claim 56). Schultz et al. does not specifically disclose the composition comprising a cladribine to cyclodextrin ratio from about 1:10 to about 1:16 (instant claims 6, 7, 10, 61, 62 and 65), or a ratio of about 1:14 (instant claims 8 and 63) or about 1:11 (instant claims 9 and 64). Schultz et al. does not specifically disclose the complex wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b) (instant claims 12 and 66). Schultz et al. does not specifically disclose the product-by-process wherein 12.00 parts by weight of cladribine and 172.50 parts by weight of hydroxypropyl-β-cyclodextrin are introduced in step (i) of the process (instant claim 91 and 93), to give a cladribine to cyclodextrin ratio of 1:14.38. Schultz et al. does not specifically disclose the product-by-process wherein 16.35 parts by weight of cladribine and 172.50 parts by weight of the hydroxypropyl-β-cyclodextrin are introduced in step (i) of the process (instant claim 92), to give a cladribine to cyclodextrin ratio of 1:10.55.

Pitha teaches a pharmaceutical combination of drug and amorphous cyclodextrin to give a stable amorphous state that improves dissolution properties of the drug and absorption by the body (column 1, lines 10-15) and that prevents crystallization processes within the pharmaceutical preparation (column 1, lines 20-25). Pitha teaches the embodiment wherein the amorphous cyclodextrin is hydroxypropyl-beta-cyclodextrin (table 1 spanning columns 3 and 4). Pitha teaches the product made

by freeze-drying, or lyophilizing, a solution of cyclodextrin and drug (column 7, lines 5-40).

Loftsson J Pharm Sci 2002 teaches drug/cyclodextrin complexes self-associate to form water-soluble aggregates as non-inclusion complexes in addition to formation of the inclusion complex (abstract). Loftsson J Pharm Sci 2002 teaches the formation of only the drug/cyclodextrin inclusion complex is a general assumption (page 2307, section Introduction), and that drug/cyclodextrin complexes self-associate to form water-soluble aggregates as non-inclusion complexes (page 2315, section Conclusions).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine Schultz et al. in view of Pitha and in view of Loftsson J Pharm Sci 2002. Schultz et al. teaches solid formulations for oral administration of cladribine and cyclodextrin. One of ordinary skill in the art would have been motivated to combine Schultz et al. in view of Pitha because Schultz et al. teaches undesirable recrystallization of cladribine in tissue may occur and damage the surrounding tissue and that complexes with cyclodextrin are known to solubilize the compound and Pitha teaches the pharmaceutical combination of drug and amorphous cyclodextrin to give a stable amorphous state that improves dissolution properties of the drug and absorption by the body. One of ordinary skill in the art would have a reasonable expectation of success in combining Schultz et al. in view of Pitha because Pitha teaches a application of a wide variety of drugs in the complex taught by Pitha and Schultz et al. teaches the formation of the cladribine and cyclodextrin complex in solution. Schultz et al. in view of Pitha and in view of Loftsson J Pharm Sci 2002 does not teach the specific cladribine to

cyclodextrin ratios of 1:14.38 or 1:10.55, however these ratios are encompassed by the prior art and Schultz et al. teaches it is within the level of skill in the art to optimize the ratio of cyclodextrin relative to cladribine (column 4, lines 35-45). See also MPEP 2144.05 II.A, "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical." One of ordinary skill in the art would be motivated to optimize the cladribine to cyclodextrin ratio to give the composition comprising no significant amount of free crystalline cladribine therein because Schultz et al. teaches undesirable recrystallization of cladribine in tissue may occur and damage the surrounding tissue (Schultz et al. column 2, lines 1-15).

Loftsson J Pharm Sci 2002 provides evidence that the property of self-association of the drug/cyclodextrin complex is necessarily present in the drug/cyclodextrin composition taught by Schultz et al. in view of Pitha. Therefore there is reasonable evidence to conclude that the process of self-association of the drug/cyclodextrin complex at the ratio taught by Schultz et al. in view of Pitha would necessarily result in both inclusion complexes and non-inclusion complexes and wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b). See also MPEP 2112.

Claims 82-90 and 94-98 are drawn to a product-by-process. The disclosed product is substantially identical to the instantly claimed product-by-process, a pharmaceutical solid oral dosage form comprising an amorphous inclusion complex of

cladribine and cyclodextrin and a non-inclusion complex of an amorphous cladribine and an amorphous cyclodextrin as detailed above. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted) (Claim was directed to a novolac color developer. The process of making the developer was allowed. The difference between the inventive process and the prior art was the addition of metal oxide and carboxylic acid as separate ingredients instead of adding the more expensive pre-reacted metal carboxylate. The product-by-process claim was rejected because the end product, in both the prior art and the allowed process, ends up containing metal carboxylate. The fact that the metal carboxylate is not directly added, but is instead produced in-situ does not change the end product.). See MPEP 2113.

Response to Applicant's Remarks:

Applicant's Remarks, filed 16 Dec 2009, have been fully considered and not found to be persuasive in view of the new grounds of rejection.

Applicant's note that the invention disclosed by Schultz et al. via a melt-extrusion process results in the formation of the mixture and not a complex of cladribine and cyclodextrin in solid form, as provided by evidence in Van Axel Castelli et al. However, MPEP 2121.01 II. provides a non-enabling reference may qualify as prior art for the

purpose of determining obviousness under 35 U.S.C. 103. Schultz et al. discloses the melt-extrusion as one method of preparing solid oral dosage forms (col 5, line 50), thus the teaching of Schultz et al. does not teach away from the combination of Schultz et al. in view of Pitha, teaching a product made by freeze-drying, and in view of Loftsson J Pharm Sci 2002 to support a conclusion of obviousness.

Conclusion

No claim is found to be allowable.

This Office Action details new grounds of rejection not necessitated by Applicant's Amendment. Therefore this Office Action is Non-Final.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jonathan S. Lau whose telephone number is 571-270-3531. The examiner can normally be reached on Monday - Thursday, 9 am - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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